PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/000726	14.05.2004	16.05.2003

International Patent Classification (IPC) or both national classification and IPC
A61P25/00, A61P23/00, A61K39/395, A61K31/00, G01N33/48

Applicant
UNIVERSITE LAVAL

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-21,31,33,35-43,53-81(IA);1-15,17,19,21-38,40,42,53-58,60,62,64,81 (all partially; N,IE,IA)

because:

☒ the said international application, or the said claims Nos. 1-21,31,33,35-43,53-81 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-15,17,19,21-38,40,42,53-58,60,62,64,81 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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International application No.
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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	44-52, 65-81
	No:	Claims	1-43, 53-64
Inventive step (IS)	Yes:	Claims	44-52,65-81
	No:	Claims	1-43,53-64
Industrial applicability (IA)	Yes:	Claims	22-30, 32,34,44-52
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
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Item III

III.1 With respect to claims 1-15, 17, 19, 21-38, 40, 42, 53-58, 60, 62, 64, and 81

Claims 1-15, 17, 19, 21-38, 40, 42, 53-58, 60, 62, 64, and 81 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved,

1. decreasing an intracellular chloride level (claims 1, 11, 22, 27, 33, 34, 53, 81)
2. modulating the activity or expression of a chloride transporter (claims 2, 12, 23, 28, 35, 54)
3. increasing the KCC2 activity or expression (claims 4, 14, 25, 30, 37, 56, 57)
4. inhibiting the TrkB (claims 15, 38, 58)
5. inhibiting the PKA (claims 17, 40, 57) or
6. inhibiting the CAM kinase (claims 19, 42, 62)

which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Although the effects can be measured, the skilled person is not in the position without undue burden to screen all known and even yet to be discovered compounds used for the treatment of pain as to their effect on intracellular chloride levels.

This afore mentioned defect is such that it has not been possible to carry out a meaningful search on the whole subject-matter. Thus the search, and therefore the examination has been limited to compounds explicitly disclosed in the application. However, in view of large number thereof and of te lack of any structural feature common to all of these compounds the search could not be limited to all of them (Article 6 PCT, lack of concisness). Moreover, for the compounds disclosed on p. 24 l. 15-22, no data are provided as to their effect on chloride levels in neuronal cells (Article 6 PCT, lack of support). Hence the search, and therefore the examination have been limited to the follwoing compounds:

(I) inhibitor of TrkB: K-252a, anti-TrkB antibodies, N-ethylmaleimide, staurosporine as disclosed in claims 16, 39, 59, and p. 23 l. 14-32

(ii) inhibitor of PKA: H-89 as disclosed in claims 18, 41, 61, and p. 23 l. 32 - p. 24 l. 4

(iii) inhibitor of CAM kinase: KN-93 as disclosed in claims 20, 43, 63, and p. 24 l. 4-10

(iv) anti-sense KCC2 mRNA as disclosed in the Example 2 of the application.

The compounds (I), (ii), and (iii) are disclosed further on p. 3 l. 25-31, p. 5 l. 10-17,

p. 7 l. 17-24, Examples 2-4).

III.2 With respect to claims 1-21, 31, 33, 35-43, and 53-81

Claims 1-21, 31, 33, 35-43, and 53-81 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(l) PCT).

Item V

V.1 Reference is made to following documents

D1: US2002028779 (HIGH ET AL.) 07 March 2002 (2002-03-07)

D2: WO02102232 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 27 December 2002 (2002-12-27)

D3: K.O. A' EY & J.D. LEVINE: 'Role of protein kinase A in the maintenance of inflammatory pain', THE JOURNAL OF NEUROSCIENCE, 15 March 1999 (1999-03-15), vol. 19, no. 6, pages 2181-2186

D4: X.Y. HUA ET AL.: 'Inhibition of spinal protein kinase C reduces nerve injury-induced tactile allodynia in neuropathic rats', NEUROSCIENCE LETTERS, 1999, vol. 276, pages 99-102

D5: L. FANG ET AL.: 'CaMK II signaling in central senzitization in a rat model of visceral pain', SOCIETY FOR NEUROSCIENCE ABSTRACTS, 2001, vol. 27, no. 2, page 2163 & 31st Annual Meeting of the Society for Neuroscience, San Diego, California, USA; November 10-15, 2001

D6: US2004032870 (RINAT NEUROSCIENCE CORP) 22 April 2004 (2004-04-22)

D7: J.A.M. COULL ET AL.: 'Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain', NATURE, 21 August 2003 (2003-08-21), vol. 424, pages 938-942

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims 1-16, 21-39, 53-59, and 64

Document D1 describes the treatment of pain using the Trk inhibitor K-252a (paragraph [0010]-[0012], [0023], [0028]-[0029], [0041],[0050]-[0051]; Example 2; claims 2, 12, 19). Therefore, the subject-matter of claims 1-16, 21-39, 53-59 and 64

is not considered novel in the sense of Article 33(2) PCT, since a newly identified mode of action, which is in the present case decreasing the intracellular chloride level, is not a feature which confers novelty on a medical use.

V.2.2 With respect to claims 1-13, 17, 18, 21-37, 40, 41, 53-57, 60, 61, and 64

Document D2 describes the use of the PKA inhibitor H-89 in combination with inhibitors of the Ras-MEK-ERK cascade for the treatment of pain, e.g. hyperalgesia, neuropathic pain and inflammatory pain (p. 7 l. 4-8, p. 3 l. 1-2, p. 10 l. 20-23, p. 14 l. 7-9, claim 94, p. 56 l. 17-20). Furthermore, D2 describes production of hyperalgesia through the activation of PKA (p. 41 l. 15-28) and document D3 describes the use of PKA inibitors for the reduction of hyperalgesia (abstract).
Document D4 describes the use of H-89 having anti-allodynic activity (abstract).
Therefore, the subject-matter of claims 1-13, 17, 18, 21-37, 40, 41, 53-57, 60, 61, and 64 is not considered novel in the sense of Article 33(2) PCT.

V.2.3 With respect to claims 1-7, 9, 11-13, 19-37, 42, 43, 53-57, and 62-64

Document D5 describes the use of KN-93 for the treatment of visceral pain (abstract).
Therefore, the subject-matter of claims 1-7, 9, 11-13, 19-37, 42, 43, 53-57, and 62-64 is not considered novel in the snese of Article 33(2) PCT.

V.2.4 With respect to claims 44-52, and 65-81

None of the documents cited in the international search report describe a method of identifying or characterizing a compound for the treatment or prevention of pain comprising the determination of the intracellular chloride level and a method for diagnosing or prognosticating pain associated with CNS dysfunction comprising the determination of the intracellular chloride level. Therefore, the subject-matter of claims 44-52 and 65-81 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 44-52 and 65-81

None of the documents cited in the international search report suggest that the determination of the intracellular chloride level might be the basis of the identification of compounds being beneficial in pain treatment or diagnosis. Therefore, the subject-matter of claims 44-52 and 65-81 is considered inventive in the sense of Article 33(3) PCT.

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V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-23 and 25

The subject-matter of claims 22-30, 32, 34, 44-52 appears to be susceptible of industrial application.

V.4.2 With respect to claims 1-21, 31, 33, 35-43, 53-81

The subject-matter of claims 1-21, 31, 33, 35-43, 53-81 is considered to be a method of treatment by therapy of the human or animal body and/or a diagnostic method practised on the human/animal body.

For the assessment of the present claims 1-21, 31, 33, 35-43, 53-81 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.5 Further remarks

V.5.1 With respect to claim 3

The abbreviation "KCC2" used in the claims should be spelled out at least once, e.g. in claim 3, in order to avoid a lack of clarity (Article 6 PCT).

V.5.2 With respect to claims 21 and 64

The term "substantially identical" used in claims 21 and 64 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

Item VI

VI.1 With respect to documents D6-D7

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited

documents D6-D7 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the document D6 could be relevant to the question of novelty.